Document title	**Clinical Study Report Synopsis**
Study title	**Effects of three oral dosages of S 44121 on cardiac arrhythmia during exercise testing in patients with catecholaminergic polymorphic ventricular tachycardia type 1.** **A 3-day, single-blind, international multicentre study.**
Study drug	**S 44121**
Studied indication	**Catecholaminergic polymorphic ventricular tachycardia type 1**
Development phase	**Phase II**
Protocol code	**CL2-44121-005**
Study initiation date	**16 February 2010**
Study completion date	**21 January 2011**
Main coordinator	[redacted] **ITALY**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 16 March 2012**

~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study:
Effects of three oral dosages of S 44121 on cardiac arrhythmia during exercise testing in patients with catecholaminergic polymorphic ventricular tachycardia type 1.
A 3-day, single-blind, international multicentre study.
Protocol No. CL2-44121-005.

International coordinator:
[redacted] Italy.
National coordinators:
[redacted] France.
[redacted]
Finland.

Study centres:
The study was conducted in 3 centres located in 3 countries: Italy (one centre, 2 included patients), France (one centre, 5 included patients) and Finland (one centre, 7 included patients).

Publication (reference): Not applicable

Studied period: Initiation date: 16 February 2010 Completion date: 21 January 2011	**Phase of development of the study: II**

Objectives: The objective of this study was to assess the effects of three single oral administrations of S 44121 on the occurrence of cardiac arrhythmia during standardized exercise tests (ETs) in patients with CPVT type 1. The safety profile of S 44121 was also evaluated.

Methodology:
This study was a phase II, single-blind, multicentre, international study. The study was made up of 3 periods:
- Screening period: during this period a selection visit (SEL) and an inclusion visit (V000) were performed. The selection visit could be performed up to 4 weeks before the inclusion visit. At least 2 baseline ETs were performed: the last two baseline ETs were the so called *qualifying ETs*. The inclusion visit could be performed on the day before visit V001 or on the same day as visit V001. Placebo was administered during the selection visit. No study treatment was administered during the inclusion visit.
- Treatment period: this period included 2 visits on two consecutive days (visits V001 and V002), during which different single oral doses of study drug were administered. One ET was performed 2 hours after each study drug administration during visit V001 (500 mg and 1000 mg). One ET was performed 2 hours after the 1500 mg study drug administration during visit V002.
- Run-out period: this period corresponded to visit V-End and was performed on the day after visit V002 (*i.e.* on Day 3). Alternatively, the patient could also be discharged at the end of Day 2 if considered appropriate following the investigator's judgement of the clinical situation of the patient (visit V-End performed at the end of Day 2). No study treatment was administered during visit V-End.

The patient was blinded regarding the sequence of the study treatment administration.

Number of patients:
Planned: 16 patients.
Included: 14 patients.

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Diagnosis and main criteria for inclusion:

Male or female, aged 18 years or more; established diagnosis of CPVT type 1 that included both ECG-documented exercise-induced cardiac arrhythmia, and genetic screening showing at least one RyR2 mutation; treated with beta-blocker at a dosing regimen that was considered optimal (associated with an individually optimized suppression of CPVT signs and symptoms, and tolerated by the patient) by the investigator.

At selection, patients should meet positivity and stability criteria regarding the occurrence of cardiac arrhythmia during the ET. For this purpose, two options applied: presence of bidirectional or polymorphic ventricular tachycardia and persistence of the arrhythmia on two consecutive ETs (option 1), or presence of at least 40 premature ventricular complexes (PVCs) during the complete ET and less than 50 % difference in the total number of PVCs between two consecutive ETs (option 2).

Study drug:

S 44121, sachet sets containing study drug at 500, 1000 and 1500 mg, respectively. The contents of each sachet set diluted in 200 mL of water should be ingested per patient 2 hours after a standard meal and beta-blocker intake (minimum delay 1.5 hours).

Batch No. L0031458.

Reference product:

Not applicable.

Duration of treatment:

Selection visit: single oral administration of placebo.

Visit V001: single oral doses of study drug were administered (500 mg in the morning and 1000 mg in the afternoon).

Visit V002: single oral dose of study drug was administered (1500 mg in the morning).

Criteria for evaluation:

Efficacy measurements:

The following measurements were performed at visits SEL, V001 and V002:

On ECG review:

- PVCs observed during the ET (Total number of PVCs, number of PVCs per minute, total number of PVCs during the worst minute, time to first event/time to disappearance).
- The ventricular salvoes (at least 3 consecutive PVCs) during the ET.
- The occurrence of individual cardiac arrhythmias during the ET.
- The sinus rate threshold of the occurrence and disappearance of individual cardiac arrhythmias during the ET (bpm).
- Total test duration of ET.

Safety measurements:

- Adverse events recording at each visit from selection to the V-End visit.
- Blood clinical laboratory parameters (hematology and biochemistry) at baseline and at the V002 visit (before S 44121 1500 mg intake).
- Resting ECG recorded at each study visit (during the minute preceding the ET, *i.e.* 2 hours after study drug intake for the visits concerned).
- Physical examination and vital signs during each study visit, including systolic and diastolic blood pressure.
- Implanted Cardioverter Defibrillator (ICD) programming review.

Pharmacokinetic measurements:

Blood samplings to determine the PK profile of S 44121 were performed during visits V001 and V002. During the treatment period, each patient was sampled three times per dose:

- Pre-dose, between 0.5 and 1 hour, and 3 hours after each study drug intake at visit V001.
- Pre-dose, between 0.5 and 1 hour, and 3 hours after study drug intake at visit V002.

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Statistical methods:

Efficacy analysis:

Efficacy analyses were provided on the Full Analysis Set. Descriptive statistics were performed on either Exercise period, or Recovery period, or both periods of the ET depending on the criterion. The treatment effect was assessed on the basis on the common time window between ET.

Safety analysis:

Safety analyses were provided on the Safety Set. Descriptive statistics were performed.

Listings regarding responders defined as patients with a decrease in number of PVCs/min ≥ 20% observed on 2 consecutive ETs: total number of PVCs (common time window), total number of PVCs/min (common time window), ET duration, number of PVCs/min (worst minute) and number of ventricular salvoes were provided as complementary (unplanned) analyses**.**

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

		S 44121
Included		14
Lost to Follow-up		-
Withdrawn		-
Completed the study	n (%)	14 (100%)
Full Analysis Set (FAS)	n (%)	14 (100%)

A total of 14 patients were selected and included in this study. They received successively 500 mg and 1000 mg of S 44121 at V001 (day 1) and 1500 mg of S 44121 at V002 (day 2). All patients completed the study. The patients were aged from 18 to 63 years old with a mean of 41.6 ± 14.9 years. There were 6 men and 8 women.

All patients suffered from catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT 1). At time of diagnosis, patients were on average 33.0 ± 15.4 years old. The mean duration of disease since diagnosis was 8.2 ± 6.0 years (median = 7 years). A RyR2 mutation was present for each patient. Overall, 11 patients had a family history of CPVT 1.

Initial clinical presentation of CPVT 1 was mainly syncope (12 patients, 85.7%). At time of symptom onset, the patients were on average 20.0 ± 15.6 years old (median was 13.5 years).

All patients presented cardiac arrhythmia induced by exercise and 10 patients also suffered from cardiac arrhythmia induced by emotion.

On resting ECG, the mean HR was of 55.4 ± 11.0 bpm. Mean values of PR interval and QRS duration were 159.3 ± 25.7 ms and 82.7 ± 13.6 ms, respectively; mean values of QTc Bazett and QTc Fridericia intervals were 389.6 ± 49.5 ms and 395.1 ± 42.5 ms, respectively. Sitting SBP / DBP values were on average 111.1 ± 15.7 mmHg / 71.6 ± 11.8 mmHg, respectively.

As required in the protocol, all patients received a beta-blocker: bisoprolol (5 patients who had doses from 0.067 mg/kg to 0.140 mg/kg daily *i.e.* from 5 mg to 10 mg daily), nadolol (4 patients who had doses from 0.650 mg/kg to 4.571 mg/kg daily *i.e.* 40 mg to 320 mg daily), propranolol (3 patients who had doses from 1.500 mg/kg to 2.667 mg/kg daily, *i.e.* 120 mg to 160 mg daily) and atenolol (2 patients who had doses of 0.263 mg/kg and 0.806 mg/kg daily, respectively *i.e.* 25 mg and 75 mg daily).

Two patients had an implantable cardioverter-defibrillator (ICD).

A total of 8 patients (57.1%) reported at least one medical history other than CPVT 1; the most frequently reported was headache in 4 patients (28.6%).

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SUMMARY – CONCLUSIONS (Cont'd)
STUDY POPULATION AND OUTCOME (Cont'd)

Exercise tests were performed on bicycle under continuous ECG monitoring, by each patient at selection. All included patients fulfilled the criteria related to positivity and stability, according to the investigator: 13 patients had at least 40 PVCs during both ET baseline 1 and 2, with a difference (in number of PVCs) between both ET ≤ 50%; furthermore, 1 patient had polymorphic and bi-directional VT at both baseline 1 and 2.
The total test duration from 120 to 820 sec with a mean of 547.0 ± 172.0 sec (median = 594.0 sec) over the exercise period and from 480 to 534 sec with a mean of 490.8 ± 16.9 sec (median = 480.0 sec) over the recovery period

At baseline, over the exercise period (over common time window), the patients had on average 77.7 ± 46.7 PVCs (median = 57.5), number of PVCs ranging from 31 to 185. The time to the first event of PVC ranged from 27 to 523 sec (mean time = 380.2 ± 143.5 sec with median = 436.5 sec). Ventricular salvo occurred in 4 patients, with a mean number of 5.5 ± 1.9. The first ventricular salvo lasted on average 1.6 ± 0.9 sec (median = 1.0 sec) and the longest event 2.0 ± 1.0 sec.
Over the recovery period (over common time window), the mean number of PVCs was 59.8 ± 75.4 (median = 13.5). Ventricular salvo occurred in 4 patients, with a mean number of 3.8 ± 3.4. The longest ventricular salvo lasted on average 6.8 ± 11.5 sec (median = 1 sec).

All ventricular salvoes recorded at baseline were ventricular tachycardia. All first (over exercise period) and longest (over exercise and recovery periods) VT at baseline were polymorphic, non-sustained, non bidirectional tachycardia, and without torsade de pointes.
One patient presented, in addition to ventricular tachycardia, supraventricular tachycardia over the exercise period, and atrial fibrillation/atrial flutter over the recovery period.

The sinus rate threshold for the occurrence of cardiac arrhythmia was on average 110.4 ± 14.2 bpm for PVC (n = 14 patients) and 130.2 ± 16.3 bpm for ventricular salvoes/VT (n = 5 patients) during the exercise period. The sinus rate threshold for the disappearance of these cardiac arrhythmia during the recovery period was on average 86.9 ± 17.9 bpm for PVC (n = 14 patients) and 113.0 ± 37.1 bpm for ventricular salvoes/VT (n = 4 patients).

The treatment compliance was assessed by recording the times of study treatment intake in the CRF: all patients received the dose of study treatment planned.

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EFFICACY RESULTS

- PVCs

Over the exercise period (during the common time window), the mean total number of PVCs decreased after each S 44121 dose intakes, except after S 44121 1000 mg intake. The mean number of PVCs per minute decreased after each S 44121 dose intakes, without relevant difference regarding the dose of S 44121.

PVCs (common time window) - Exercise period – FAS
Change from baseline to each post baseline measurement
Restricted to patients having at least one event at baseline or at the post-baseline visit

Total number of PVCs		**S 44121**
Baseline value	n_{obs}	14
	Mean ± SD	77.7 ± 46.7
	Median	57.5
	Min ; Max	31 ; 185
V001a (500 mg) - Baseline	n_{obs}	14
	Mean ± SD	-16.2 ± 57.8
	Median	-17.5
	Min ; Max	-139 ; 74
V001b (1000 mg) - Baseline	n_{obs}	14
	Mean ± SD	1.3 ± 51.0
	Median	-5.0
	Min ; Max	-104 ; 103
V002 (1500 mg) - Baseline	n_{obs}	14
	Mean ± SD	-6.2 ± 70.3
	Median	-16.5
	Min ; Max	-127 ; 168
Number of PVC per minute		
Baseline value	n_{obs}	14
	Mean ± SD	12.13 ± 12.88
	Median	6.60
	Min ; Max	3.1 ; 51.8
V001a (500 mg) - Baseline	n_{obs}	14
	Mean ± SD	-4.37 ± 14.21
	Median	-2.15
	Min ; Max	-51.8 ; 8.3
V001b (1000 mg) - Baseline	n_{obs}	14
	Mean ± SD	-3.00 ± 14.79
	Median	-0.60
	Min ; Max	-51.8 ; 11.5
V002 (1500 mg) - Baseline	n_{obs}	14
	Mean ± SD	-3.12 ± 15.47
	Median	-1.95
	Min ; Max	-51.8 ; 18.7

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EFFICACY RESULTS (Cont'd)

- **PVCs (Cont'd)**

After S 44121 intake, a trend to decrease was observed in total number of PVCs during the worst minute, over the exercise period (on average -6.1 ± 18.1, -4.0 ± 21.1 and -3.4 ± 18.7, after S 44121 500 mg, 1000 mg and 1500 mg, respectively).

Time to first PVC increased after each S 44121 intake compared to baseline: on average 30.4 ± 106.3 sec (median = 13.5 sec) after S 44121 500 mg intake, 32.4 ± 89.4 sec (median = 23.0 sec) after S 44121 1000 mg intake and 21.9 ± 69.4 (median = 19.5 sec) after S 44121 1500 mg intake.

Over the recovery period and during common time window, the mean total number of PVCs decreased after each S 44121 dose intake without relevant difference between dose groups.

- **Ventricular salvoes**

Over the exercise period, 5 patients experienced ventricular salvo at baseline. After both S 44121 500 mg and 1000 mg intake, 2 had no more ventricular salvo and 3 patients still reported ventricular salvo; after S 44121 1500 mg intake, the 5 patients still reported ventricular salvo. All longest ventricular salvo experienced by these patients were polymorphic at both baseline and post-baseline assessment.

- **Individual cardiac arrhythmias**

As all ventricular salvoes recorded during the study were ventricular tachycardia (VT), results regarding VT were similar to those regarding ventricular salvoes. At both baseline and post baseline assessments, all VT (1st or longest event) were non-sustained, not bi-directional and no torsade de pointe was recorded.

Regarding other arrhythmias over the exercise period, SVT was reported for one patient at baseline and after each S 44121 intake and atrial fibrillation (duration of 2 sec) was reported for one patient after S 44121 1500 mg intake without AF at baseline.

- **Sinus rate threshold**

Over the exercise period, sinus rate threshold for occurrence of PVCs decreased after each post baseline measurement mainly after S 44121 1500 mg dose intake (on average –9.4 ± 7.1 bpm) without dose dependency.

- **Total test duration:**

Over the exercise period, mean change in test duration was 24.0 ± 86.2 sec, 17.8 ± 92.2 sec and 23.1 ± 84.0 sec after S 44121 500 mg, 1000 mg and 1500 mg intake, respectively without relevant difference between doses and with medians at -4.5 sec, -9.5 sec and –0.5 sec, respectively.

- **Responders (unplanned analysis)**

For 4 patients (29.0%), the response to S 44121 was particularly marked in term of number of PVCs and salvoes of PVCs: one of them changed from 104 PVCs at baseline to none after each S 44121 dose intake. The favourable changes were observed across different parameters in these responder patients: PVCs, ventricular salvoes as well as exercise duration for some of them.

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SAFETY RESULTS

- **Emergent adverse events**

Overall, 5 patients (35.7%) reported 6 emergent adverse events during the overall study period in the Safety Set: 1 patient (7.1%) during the S 44121 500 mg treatment period, 3 patients (21.4%) during the S 44121 1000 mg treatment period and 1 patient (7.1%) during the S 44121 1500 mg treatment period.
These emergent adverse events were mainly related to general disorders and administration site conditions (3 patients). Emergent adverse events were the following: sinus bradycardia, headache, infusion site irritation ["local irritation of subcutaneous tissue at the site of infusion (right forearm)"], leukocytosis, application site dermatitis (related to ECG electrodes irritation, according to the investigator) and feeling hot ["hot extremities (hand and feet)"]. No emergent adverse event was reported more than once.
All emergent adverse events were rated as mild (4/6 events) or moderate (2/6 events); none of them was considered as related to the study drug or due to a lack of efficacy or subsequent to study drug discontinuation.
No emergent adverse events led to treatment discontinuation. All but one event (mild leucocytosis without available assessment after V002) recovered at the end of the study.

Neither deaths nor serious adverse events occurred during the study.

- **Laboratory parameters**

Regarding biochemical and haematological parameters, no clinically relevant changes over time was observed during the study. Emergent out-of-reference range values were sparse; only one patient had an emergent Potentially Clinical Significant Abnormal value: low haematocrit (0.31) at V002 with a baseline value at 0.37.
One patient reported abnormal value (not PCSA), considered as clinically significant by the investigator: high white blood cell count value (10.6 G/L) at V002 (baseline value was high at 8.5 G/L) associated with high value of monocytes (0.81 G/L) (baseline value was normal at 0.64 G/L): the investigator reported a mild leucocytosis as adverse event, unlikely related to study drug but to concomitant treatment by prednisolone (20 mg daily per os, during few days for worsening of asthma) according to the investigator.

- **Vital signs**

No clinically relevant change over time was observed regarding mean sitting blood pressure. One patient changed from 120 mmHg at baseline to 150 mmHg at V002 for SBP and from 90 mmHg at baseline to 100 mmHg at V002 for DBP; SBP and DBP were normalised at V-End (127 mmHg and 85 mmHg, respectively). No patient, except one, had a SBP ≤ 90 mmHg after baseline: patient 005 250 0701 00028 reported SBP of 90 mmHg at V002 with a baseline value equal to 100 mmHg and SBP returned to 100 mmHg at V-End.

- **Electrocardiogram**

Regarding ECG parameters, no clinically relevant changes over time were observed.
Overall, 2 patients reported an emergent ECG non clinically significant abnormality: sinus bradycardia and junctional rhythm. In addition, one patient reported a sinus bradycardia present at each visit from selection to V-End, which became clinically significant at V002, according to the investigator.

CONCLUSION

In conclusion, this exploratory, single-blind, international multicentre study conducted in 14 patients with CPVT type 1 treated by beta-blockers and by sequentially oral doses (500, 1000 and 1500 mg) of S 44121 over 2 days, showed a trend to improvement in term of number of premature ventricular complexes and time to first event. No dose dependency was noted. For 4 patients, the response was specifically marked. Regarding safety profile, S 44121 was well tolerated.

Date of the report: 16 March 2012